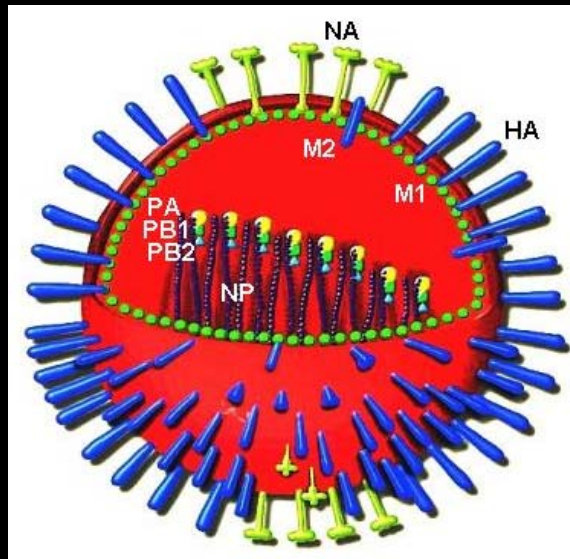


Meeting the Challenge of Annual Flu Vaccine Preparedness: FDA Activities and Perspectives



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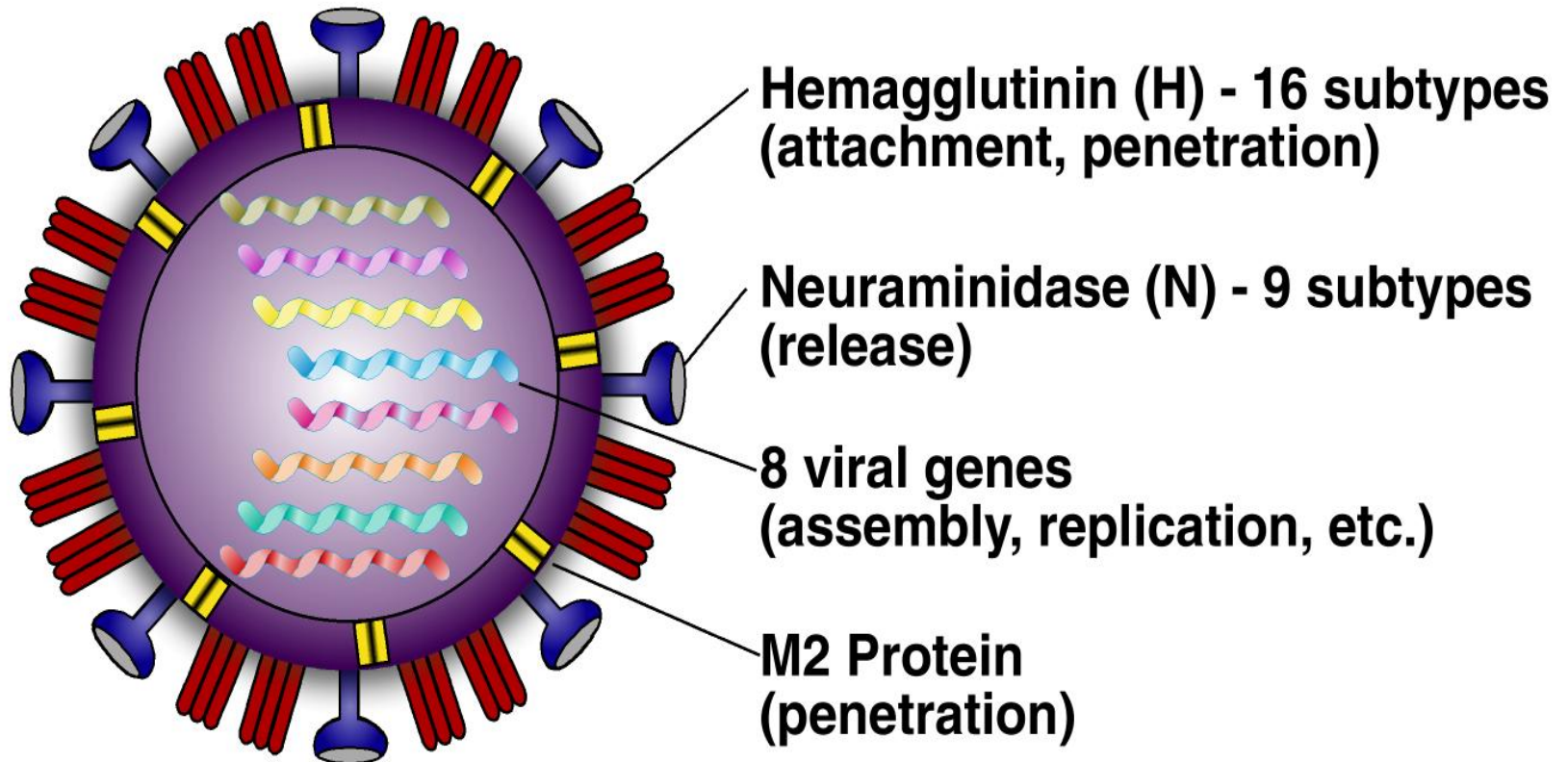
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NFID, Washington, DC, 5/18/06

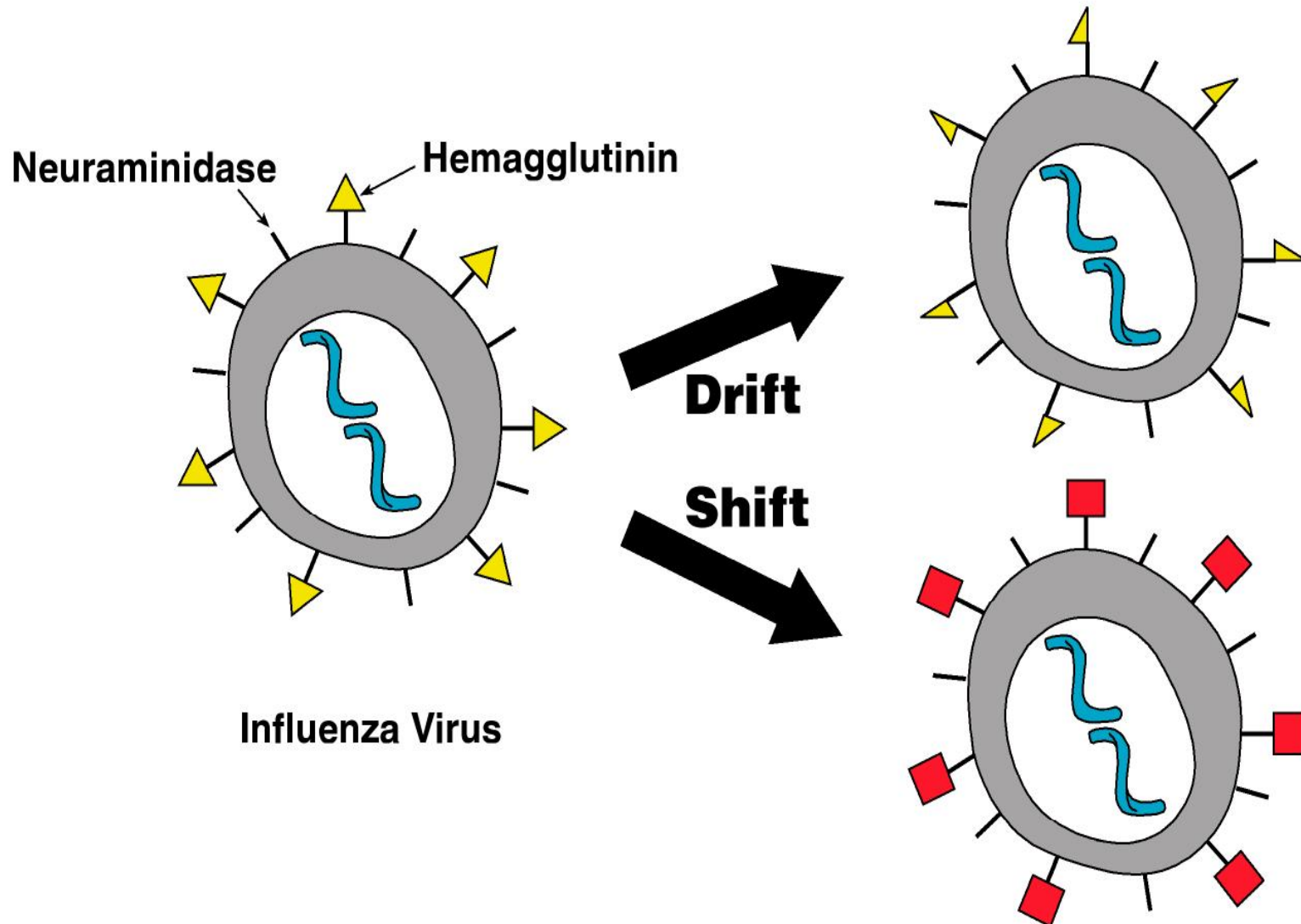
Annual Influenza Vaccine

- A new vaccine is made every year – 80-120 million doses – with intense FDA involvement
- Annual vaccines include three strains: 2 A, 1 B
- Vaccine strains are selected each year to match circulating viruses
 - Based on worldwide surveillance
 - FDA and CDC are WHO Collaborating Centers and work with WHO in strain selection. FDA makes the final decision on strains for US manufacturing
 - Surprises can occur in what strains circulate

Influenza A Virus



Influenza: Antigenic Drift and Shift



Flu Vaccines: Inactivated

- 3 manufacturers US licensed: sanofi, Chiron, GSK
- Inactivated HA vaccine made by adapting strains to grow in embryonated eggs (may be variable), then grow each of 3 strains separately, followed by inactivation & purification into "monovalents"
- The monovalents are blended in appropriate concentrations, using standards and reagents provided annually by CBER to make a final trivalent vaccine, which is then "filled & finished"
 - Early parts of process are not sterile and thus pose potential risks for contamination of manufacturing environment, of intermediaries and of final product
 - Monitoring and testing at multiple stages critical including potency, sterility, environment

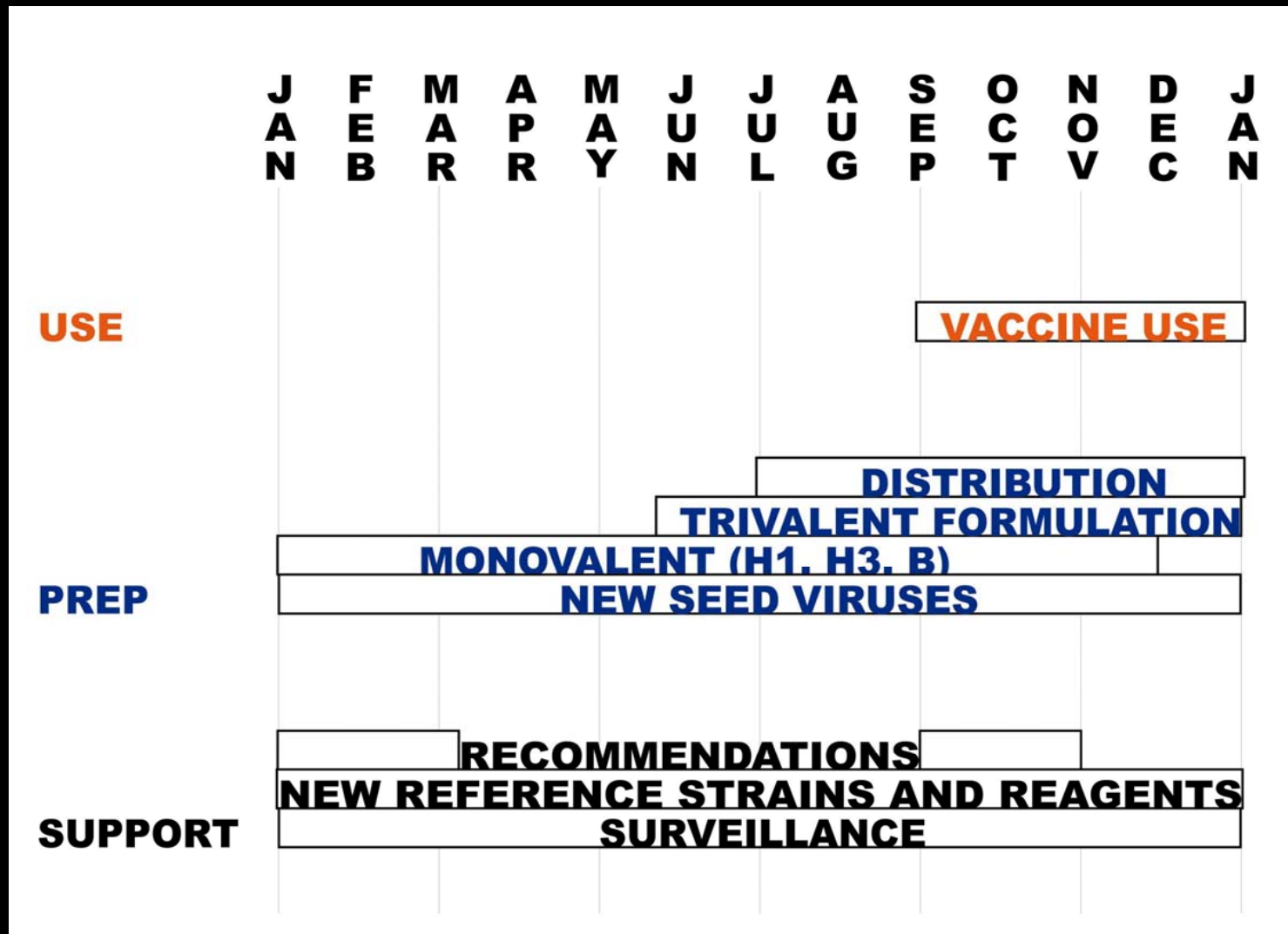
Live Attenuated Vaccine (LAIV)

- One licensed US manufacturer: MedImmune
- Live virus cold adapted and attenuated, stable
- Made in SPF embryonated eggs
- Well tolerated, efficacy well documented in children and young adults
- Potential to rapidly induce immunity vs. new and pandemic strains
- Live virus with multiple antigens likely offers increased cross protection among strains (esp. for antigenic drift)

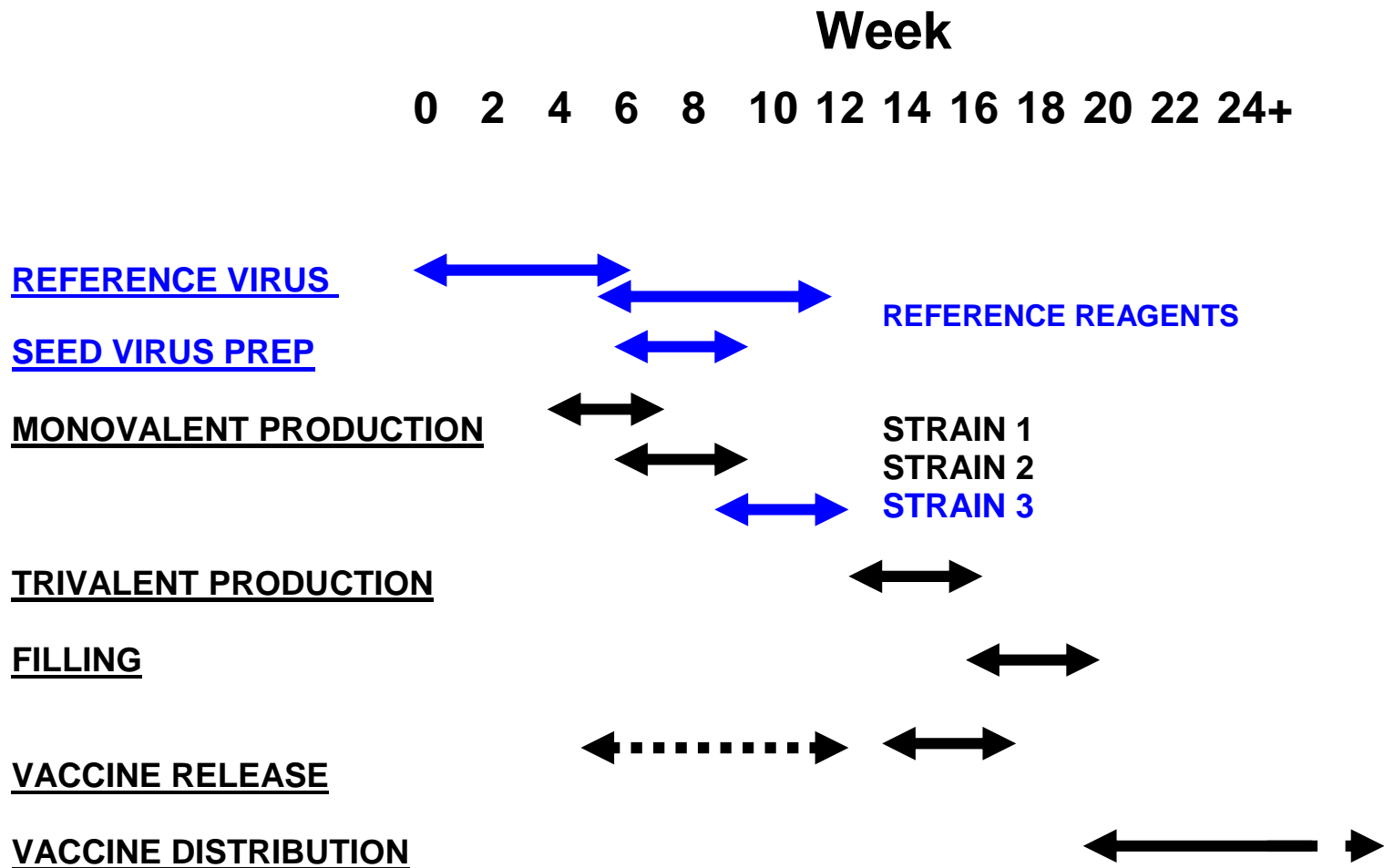
Yearly Strain Choice

- Questions:
 - Are new (drifted or shifted) influenza viruses present?
 - Are these new viruses spreading in people?
 - Do current vaccines induce antibodies against the new viruses?
 - Are strains suitable for vaccines available (known quality and safety, suitable for growth in eggs)?
- Strains for 2006-7:
 - A/New Caledonia/20/99 (H1N1)
 - A/Wisconsin/67/2005 (H3N2) (*changed from 2005-6*)
 - B/Malaysia/2506/2004 (*changed from 2005-6*)

Typical Timeline for Production



Time to Trivalent Vaccine



How does FDA contribute and what steps might speed process?

- Produce & provide high growth reassortant strains
 - *Earlier strain selection vs. higher risk in choice*
- Produce and provide antisera to measure potency & help formulate - historically have also determined potency of all monovalents
 - *Move toward manufacturer for routine testing*
 - *Need for more rapid antigen/antisera production*
 - *Need for improved potency tests*
- FDA reviews testing and production records for all lots and performs testing, as needed
 - *Need for more rapid assays, especially for sterility*
- Safety surveillance: from VAERS to HC databases



Increasing manufacturing diversity and capacity

- Markets (demand and sales) are main driver
- Expanded indications, increased demand and prices now stimulating manufacturers' interest
- 2004 US shortage and pandemic preparedness efforts have further accelerated interest
- FDA providing flexible regulatory pathways and guidance to facilitate efficient and effective development of annual and pandemic vaccines (e.g. 3/2/2006 guidances)
 - <http://www.fda.gov/cber/gdlns/trifluvac.htm>
 - <http://www.fda.gov/cber/gdlns/panfluvac.pdf>

Pathways to Speed Availability: Accelerated Approval

- FDA considers there to be a short supply
- CBER considers HI anti-HA antibody levels as a likely surrogate marker for efficacy
- Therefore, accelerated approval can be sought based on safety and immunogenicity provided post-approval studies of clinical efficacy
- Shortens approval time by 1-2 years
 - GSK 900 + person study designed and data generated/reviewed and approved in very rapid timeframe – enhancing annual vaccine supply in 2005 and pandemic preparedness
- Applicable to suitable cell culture and recombinant vaccines as well

Lessons Learned Lead to Other FDA Steps to Strengthen Supply

- Globalization:
 - Information sharing agreements and relationships
 - Pre and post-licensure
 - Encouraging global vaccine development plans and regulatory cooperation/harmonization
- Annual inspections of flu manufacturers
- GMP initiative
 - Increased communications and enhanced preventive approaches and collaborations specific to vaccine GMPs

New approaches to facilitating manufacturing and testing of pandemic vaccines can help annually

- Preparation of library of qualified seed strains and high growth reassortants representing major known and evolving antigens
- Studies of strain cross-protection in HA types, methods to predict based on sequence analysis
- Advance preparation of needed reagents for manufacturing: e.g. antigens & antisera
- Evaluation of existing assays and consideration of development of new technological approaches (e.g. to potency, Abs, sterility) that may speed manufacturing and product review/release

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- There are significant potential advantages in flexibility afforded by non-egg based technologies
- FDA has licensed other cell culture derived and recombinant based vaccines and has no special regulatory concerns with these technologies for flu
 - Potential challenges include adventitious agent and tumorigenicity evaluation for cell based vaccines and immunogenicity for recombinants, efficiency for both
 - We are encouraging their development and providing intensive interactions with sponsors –e.g. recent VRPAC on MDCK, new updated guidance on testing

Thanks!

- We interact intensively with sister agencies, WHO and manufacturers to facilitate production of a new flu vaccine yearly, providing strains, reagents, review and testing
- We are working with partners to diversify and strengthen influenza vaccine manufacturing and have provided flexible rapid regulatory pathways
- In partnership with HHS and NIH, we are fostering development of new technologies that can help speed the process and increase its capacity, resiliency and reliability
- We continually reevaluate our approach to these challenges and have updated them based on recent experience
- Investments in pandemic preparedness are likely to benefit annual flu vaccines and their manufacture and vice versa
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